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A phenomenological model for circadian and sleep allostatic modulation of plasma cortisol concentration

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Thorsley D, Leproult R, Spiegel K, Reifman J. A phenomenological model for circadian and sleep allostatic modulation of plasma cortisol concentration. *Am J Physiol Endocrinol Metab* 303: E1190–E1201, 2012. First published September 25, 2012; doi:10.1152/ajpendo.00271.2012.— Both circadian rhythmicity and sleep play significant roles in the regulation of plasma cortisol concentration by the hypothalamo-pituitary-adrenal (HPA) axis. Numerous studies have found links between sleep and changes in cortisol concentration, but the implications of these results have remained largely qualitative. In this article, we present a quantitative phenomenological model to describe the effects of different sleep durations on cortisol concentration. We constructed the proposed model by incorporating the circadian and sleep allostatic effects on cortisol concentration, the pulsatile nature of cortisol secretion, and cortisol's negative autoregulation of its own production and validated its performance on three study groups that experienced four distinct sleep durations. The model captured many disparate effects of sleep on cortisol dynamics, such as the inhibition of cortisol secretion after the wake-to-sleep transition and the rapid rise of cortisol concentration before morning awakening. Notably, the model reconciled the seemingly contradictory findings between studies that report an increase in cortisol concentration following total sleep deprivation and studies that report no change in concentration. This work provides a biomathematical approach to combine the results on the effects of sleep on cortisol concentration into a unified framework and predict the impact of varying sleep durations on the cortisol profile.

biomathematical models; hypothalamo-pituitary-adrenal axis; sleep loss

CORTISOL IS A KEY HORMONE in the regulation of human metabolism and stress response, and its dysregulation is manifested in psychological disorders such as depression and posttraumatic stress disorder (PTSD) (19, 39) and in metabolic disorders such as Cushing's syndrome (2). Cortisol is produced in the zona fasciculata of the adrenal cortex. The secretion of cortisol is regulated by adrenocorticotropic hormone (ACTH), whose release from the anterior pituitary gland is induced by the transport of corticotropin-releasing hormone (CRH) from the hypothalamus to the pituitary. The secretion of ACTH occurs in pulses (5, 21), and thus the secretion of cortisol is pulsatile as well. Cortisol is distributed through the bloodstream to the hypothalamus and pituitary and downregulates the secretion of CRH and ACTH, thereby having a negative feedback effect on its own production (38). Because the secretion of CRH is governed by signals from the suprachiasmatic nuclei in the anterior hypothalamus, the basal cortisol dynamics exhibit a significant circadian component (18, 40). The 24-h cortisol profile consists of an early morning rise, decreasing levels during the daytime, and a quiescent period centered around midnight.

The basal cortisol dynamics are also affected by sleep-wake schedules and sleep-wake transitions (6, 29). Disturbed or irregular sleep schedules can dysregulate cortisol production, and the cumulative effect of disturbed sleep can contribute to the buildup of allostatic load (25). For example, in military settings, where irregular sleep schedules are common due to operational constraints, irregular sleep can affect cortisol levels and have negative impacts on cognitive performance, mood, and stress (23).

A collection of mechanistic models has been proposed to describe the various processes of the hypothalamo-pituitary-adrenal (HPA) axis, including the neural firing of CRH (13), the effect of glucocorticoid receptor count on HPA axis stability (17), HPA axis robustness to variations in cortisol binding affinity (20), and the effect of variations in the strength of negative feedback in depression and PTSD (31). However, the existing mechanistic models of the HPA axis do not account for the effects of sleep on cortisol regulation, which are not well understood at the molecular level (11). Instead, most of the understanding of the effects of sleep duration on cortisol production is at a qualitative, phenomenological level (2). In this article, we present a phenomenological model describing the effects of sleep duration on cortisol concentration, thereby bringing together many disparate results connecting sleep and cortisol in a unified, quantitative framework. Our proposed model takes into account the pulsatile nature of cortisol secretion, the negative autoregulation of cortisol, and the circadian and sleep allostatic effects on cortisol concentration.

We based our model on the Borbély (3) two-process model of sleep regulation, where the two processes are a circadian process and a sleep homeostatic process. The sleep homeostatic process has its physiological basis in the power generated by electroencephalographic (EEG)-δ waves during slow-wave sleep. As sleep progresses, the power of successive EEG-δ wave episodes decreases exponentially. EEG-δ wave power is considered a measure of "sleep intensity," (4) and thus, in the Borbély (3) model, the sleep homeostatic process is modeled as

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a decreasing exponential during sleep. Conversely, there is a negative correlation between EEG-δ power and the rate of cortisol secretion during sleep (16); thus, we hypothesized that the rate of cortisol secretion should increase exponentially to a saturation point during sleep. There is also a positive correlation during wakefulness between EEG-β power and the rate of cortisol secretion (10). Because the increase in EEG-β power corresponds to the effects of sleep deprivation (24), we hypothesized that the rate of cortisol secretion during wakefulness follows a saturating rising exponential curve, as in the Borbély (3) model. Because our hypothesized process describing the effects of sleep timing on cortisol secretion differs from the Borbély (3) sleep homeostatic process, we refer to our process as the sleep allostatic process.

We validated the proposed model using data from two studies (22, 30) in which one study group experienced total sleep deprivation, a second group experienced 8 h of sleep, and a third group experienced both sleep restriction and sleep extension scenarios. We show that our model quantitatively captures well-established relationships between sleep and cortisol, such as the inhibition of cortisol secretion shortly after the wake-to-sleep transition (36) and the sharp increase in cortisol concentration shortly before normal waking (29). Furthermore, our model reconciles divergent findings on the effects of sleep deprivation on cortisol concentration by demonstrating when total sleep deprivation causes an increase in cortisol concentration (9, 22) and when it causes no such increase (15, 28).

MATERIALS AND METHODS

This work is a retrospective analysis of data originally reported by Leproult et al. (22) and Spiegel et al. (30). The participants in both studies were healthy young men. Both protocols were approved by the Institutional Review Board at the University of Chicago, and all participants gave written informed consent.

Leproult study (groups A and B). Before the start of the study, all participants were habituated to the laboratory environment by spending two nights in the Clinical Research Center at the University of Chicago. The participants were studied over a 32-h period, starting from 1800 on *day 1* until 0200 on *day 3*. The participants were aware of local clock time. The participants remained recumbent throughout the study and were maintained in dim light during wake periods and in complete darkness during sleep periods. Food intake was replaced by an intravenous glucose infusion at a constant rate of 5 g/kg every 24 h.

Group A consisted of 17 individuals [20–30 yr old, body mass index (BMI) means ± SE 22.7 ± 0.5 kg/m^2] who experienced total sleep deprivation during the 32-h study period. *Group B* consisted of nine individuals (22–32 yr old, BMI means ± SE 22.8 ± 1.0 kg/m^2) who experienced 8 h of time allocated for sleep (TAS) from 2300 to 0700. (Because the participants in the 2 studies were recumbent throughout, we use the phrase "time allocated for sleep" instead of the more frequently used "time in bed.") Both groups were wakened at 0700. A sterile heparin lock catheter was inserted in each individual's forearm at 1400, and starting at 1800, 1-ml blood samples were drawn at 20-min intervals for 32 h. The intravenous line was kept patent with a slow drip of heparinized saline. Plasma cortisol levels were determined using the Coat-A-Count kit (Diagnostic Products, Los Angeles, CA). The lower limit of sensitivity was 13.8 nmol/l. The intra-assay coefficient of variation averaged 5%. All samples from the same individual were analyzed in the same assay. Figure 1, *A* and *B*, shows a schematic of the Leproult study.

Spiegel study (group C). Group C consisted of 11 individuals (18–27 yr old, BMI means ± SE 23.4 ± 0.5 kg/m^2). During the week prior to the study, participants were asked to conform to fixed bedtimes (2300–0700) and mealtimes. Wrist activity was monitored to verify compliance. The subjects spent 16 consecutive nights in the Clinical Research Center, consisting of three nights of 8-h TAS (2300–0700), six nights of 4-h TAS (0100–0500), and seven nights of 12-h TAS (2100–0900). During the last 60 h of each TAS condition, the participants remained recumbent. During the last 24 h of the 4-h TAS and 12-h TAS conditions, blood was sampled at 10- to 30-min intervals starting at 0900. Participants received identical carbohydrate-rich meals (30 kcal/kg body wt, 62% carbohydrates) at 0900, 1400, and 1900 during data collection. Plasma cortisol levels were measured by RIA (Orion Diagnostica, Espoo, Finland), with a sensitivity of 20.7 nmol/l and a 4% intra-assay coefficient of variation. Figure 1*C* shows a schematic of the Spiegel et al. (30) study. *Subject 8* in *group C* required replacement of the catheter during the 4-h TAS condition and experienced a stress-related increase in cortisol concentration. As a result of this confound, this subject was removed from the analysis.

Mathematical analysis. All calculations, parameter estimations, and cross-validations were performed in MATLAB R2011B. Nonlinear least squares estimation was used for parameter estimation. For the 0- and 8-h TAS conditions, pulsatile cortisol secretion was set to begin at 0700 on *day 1*; cortisol secreted before that time was assumed to have disappeared by the time data collection started. For the 4- and 12-h TAS scenarios, secretion was set to begin at 1900 on *days 7* and *14*, respectively.

The nonlinear coefficient of determination (r^2) between a fit f(t) and a data set y(t_1), y(t_2), . . . y(t_n) was calculated as

$$r^2 = 1 - \left[\left(\sum_{i=1}^{n}\left(f(t_i) - y(t_i)\right)^2\right) / \left(\sum_{i=1}^{n}\left(y(t_i) - \bar{y}\right)^2\right)\right],$$

where $\bar{y}$ is the mean of the data set. The root mean squared error (RMSE) between the fit and the data set was calculated as

$$\mathrm{RMSE} = \sqrt{\left(\sum_{i=1}^{n}\left(f(t_i) - y(t_i)\right)^2\right) / n}.$$

RESULTS

Two-process model for cortisol secretion and concentration. We describe the rate of cortisol secretion using a two-process

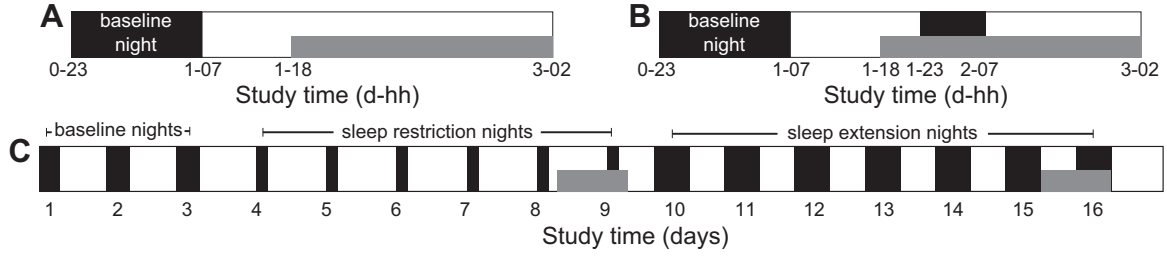

Fig. 1. Schematics of the study protocols. Black bars indicate time allocated to sleep (TAS). Gray bars indicate times when data collection occurred. *A*: protocol experienced by *group A*. *B*: protocol experienced by *group B*. *C*: protocol experienced by *group C*. During the sleep restriction nights, the TAS was from 0100 to 0500. During the sleep extension nights, the TAS was from 2100 to 0900. Data were collected for 24 h starting at 0900 on the 8th and 15th days. d-hh, day-hour (indicating that the time given on the *x*-axis is given by the day within the study followed by the 2 digits indicating the time of day; e.g., 1–18 indicates that the time is 1800 on *day 1* of the study).

model that contains both a circadian component and a sleep allostatic component. The circadian function C(t), measured in nmol/h, is defined at time t as

$$C(t) = \beta\left(\sum_{i=1}^{4} a_i \sin\left[\left(\frac{\pi i}{12} - \theta\right)t\right] + 1\right),$$

where the a_i denotes the Borbély-Achermann parameters $a_1 = 0.97$, $a_2 = 0.22$, $a_3 = 0.07$, and $a_4 = 0.03$ (4), β represents the circadian amplitude in nmol/h, and θ is the circadian phase in

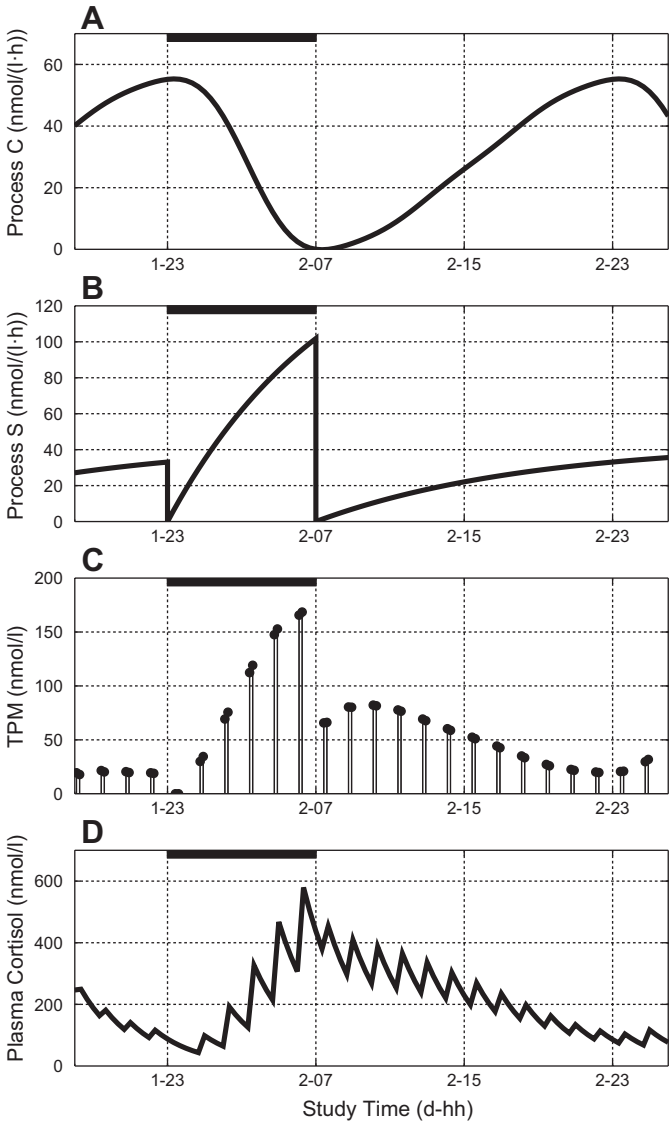

Fig. 2. Development of the two-process model (TPM) for cortisol. *A*: the circadian *process C* describes an entrained circadian rhythm governed by amplitude β and phase θ. *B*: the sleep allostatic *process S* describes the effect of sleep on the rate of cortisol production. During wake, *process S* is a rising saturating exponential governed by amplitude α_w and rate parameter γ_w. During sleep, *process S* is governed by amplitude α_s and rate parameter γ_s. *C*: the TPM generates pulses whose amplitude is defined in part by the sum of *processes S* and *C*. The magnitude of these pulses is decreased according to a proportional feedback constant, k_p. Each physiological pulse is modeled as a pair of Kronecker δ-functions occurring with a period of 80 min. *D*: plasma cortisol concentration is modeled as the sum of decaying exponential functions with cortisol disappearance rate d_c. The parameter values used in this plot are the mean parameter values for *group B*, which are shown in Table 2.

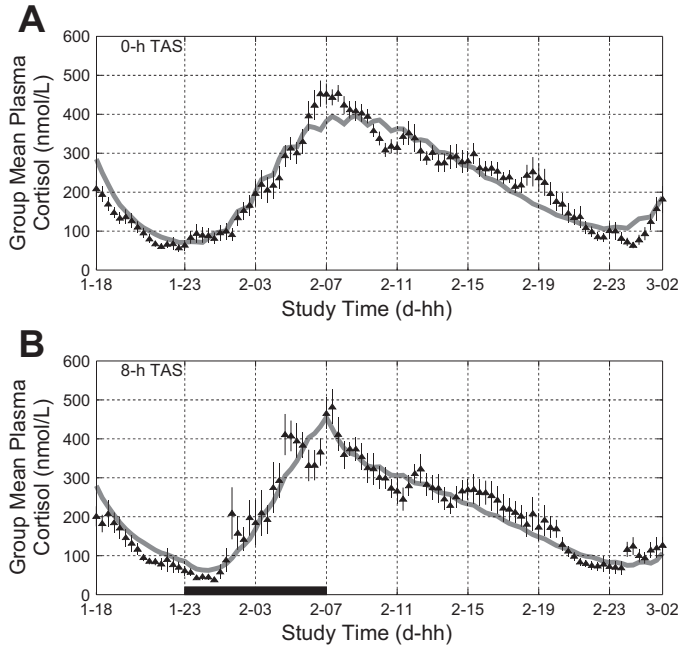

Fig. 3. *A*: group mean raw data and model fit for *group A* ($n = 17$). *B*: group mean raw data and model fit for *group B* ($n = 9$). The black bar indicates the 8-h TAS period. Both groups slept from 2300 the previous night to 0700 on study *day 1*. In the fitted mean cortisol concentration, the Mann-Whitney *U*-test showed that *group B* has a significantly lower concentration of cortisol from 2000 on *day 2* to 0000 on *day 3* ($P = 0.006$), corroborating the result in Ref. 22.

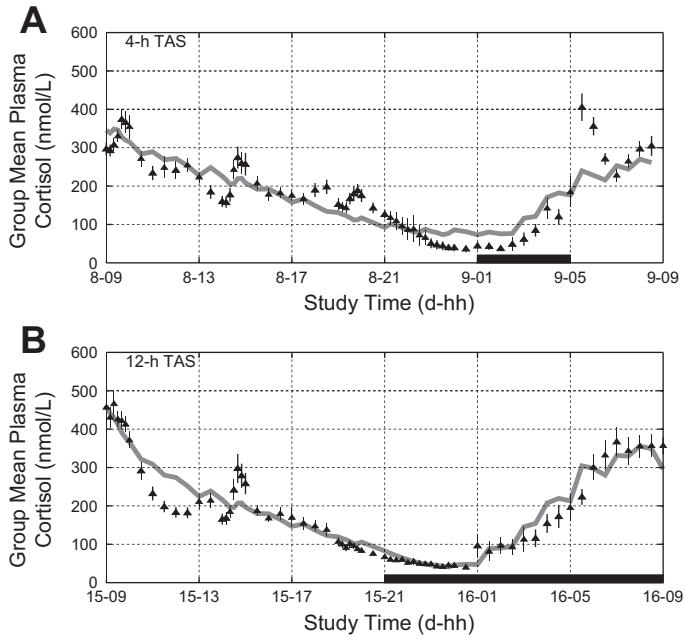

Fig. 4. *A*: group mean raw data and model fit for *group C* ($n = 10$) in the 4-h TAS scenario. Black bar indicates the TAS period. *B*: group mean raw data and model fit for *group C* in the 12-h TAS scenario. Black bar indicates the TAS period. There was a large spike in the 4-h TAS data at 0530 on *day 9* that was not captured by the model fit. We believe this spike was due to the cortisol awakening response (see DISCUSSION). There was also a saturation in the 12-h TAS data at 0730 on *day 16* that was not well captured by the model fit. This leveling off is likely due to the majority of individuals waking while remaining in sleep position.

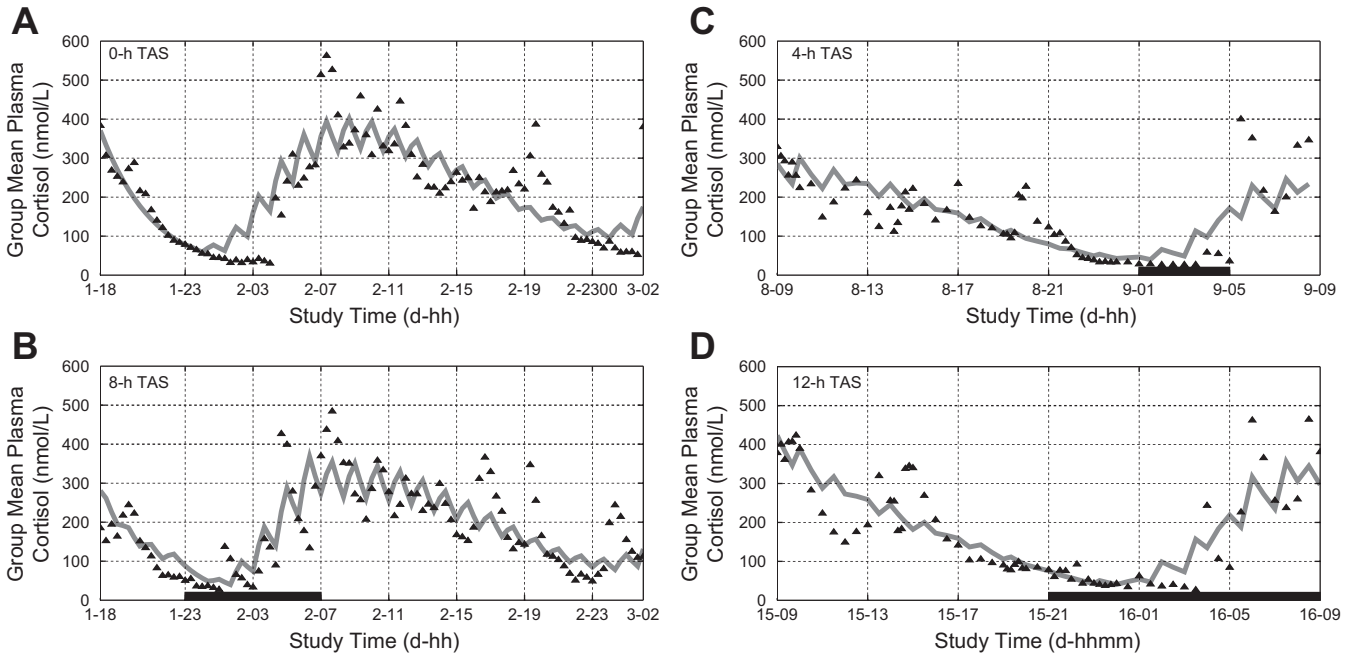

Fig. 5. Representative individual fits for the 0- (*A*), 8- (*B*), 4- (*C*), and 12-h TAS (*D*) scenarios. The individual fits demonstrated pulsatile behavior in cortisol concentration, whereas the group average fits did not. The individual fits chosen for this plot were those with the median root mean squared error among the fits for each scenario. Figures 7–10 show the full set of individual fits.

hours. The sleep allostatic function S(t), also measured in nmol/h, is piecewise continuous and consists of two saturating rising exponentials:

$$S(t) = \begin{cases} \alpha_w(1 - \gamma_w^{(t-T_{sw})}) \text{ during wake,} \\ \alpha_s(1 - \gamma_s^{(t-T_{ws})}) \text{ during sleep,} \end{cases}$$

where the parameters during wake are T_{sw}, the most recent sleep-to-wake transition time, α_w, the wake allostatic magnitude in nmol/h, and γ_w, the unitless wake allostatic rate. During sleep, the parameters are T_{ws}, the most recent wake-to-sleep transition time, α_s, the sleep allostatic magnitude in nmol/h, and γ_s, the unitless sleep allostatic rate. S(t) models a rate of secretion, which changes discontinuously at each sleep-wake transition when its value instantaneously decreases to zero. The two-process model output at time t is

$$TPM(T) = \int_{-\infty}^{\infty} \left[S(t) + C(t)\right]\delta(t - T)dt,$$

where δ is a Dirac δ-function. TPM(T) is measured in nmol/l.

Cortisol is produced in pulses. We assumed an interpulse period of 80 min (13) and modeled each physiological pulse as a pair of Kronecker δ-functions occurring 10 min apart. This allowed us to capture the situations where a cortisol measurement occurs before, after, or during a 20-min-long pulse. We assumed that the phase of the pulsatile rhythm is locked to the circadian phase, with δ-functions occurring at times $\theta + 2n + \frac{1}{12}$ and $\theta + 2n + \frac{3}{12}$, where n is any integer number of hours. We denoted the set of times at which δ-functions occur as T_δ.

The concentration of plasma cortisol y(t) at time t is defined as

$$y(t) = \sum_{T<t, T\in T_\delta} [TPM(T) - k_p y(T)]e^{-d_c(t-T)},$$

where k_p is a proportional feedback constant describing the effect of cortisol autoregulation and d_c is the cortisol disappearance rate. The concentration y(t) is modulated primarily by the changing amplitude of the secretion pulses (35). We thus modeled an individual's plasma cortisol concentration as a sum of decaying exponentials with eight parameters: circadian amplitude β and phase θ, wake allostatic amplitude α_w and rate γ_w, sleep allostatic amplitude α_s and rate γ_s, cortisol feedback constant k_p, and disappearance rate d_c. The constituent elements of the model are illustrated in Fig. 2.

To evaluate the performance of the model, we first fit the model to individual and group mean data for different sleep timing scenarios. We then determined whether the parameter values calculated for individuals in each study group are

Table 1. *Group mean and individual measurements of goodness of fit for each of the 4 study scenarios*

TAS, h	Group Mean RMSE	Mean (SD) of Individual Fit RMSE	Group Mean r^2	Mean (SD) of Individual Fit r^2
0	34.2	80.3 (21.9)	0.91	0.66 (0.10)
4	46.1	67.6 (16.7)	0.79	0.64 (0.09)
8	36.7	78.6 (20.8)	0.89	0.65 (0.11)
12	37.4	67.6 (17.5)	0.91	0.75 (0.12)

TAS, time allocated to sleep; RMSE, root mean squared error (nmol/l); r^2, coefficient of determination.

Table 2. *Means (SD) of the fitted individualized model parameters for each of the 3 study groups*

Study Group	α_w, nmol/h	γ_w	β, nmol/h	θ (Time)	d_c, l/h	k_p	α_s, nmol/h	γ_s
Group A	70.8 (34.6)	0.954 (0.025)	87.4 (17.2)	0239 (0042)	0.448 (0.061)	0.246 (0.060)		
Group B	44.2 (24.2)	0.917 (0.034)	64.1 (19.0)	0233 (0017)	0.422 (0.061)	0.169 (0.123)	173.2 (79.1)	0.895 (0.035)
Group C	26.0 (9.18)	0.902 (0.036)	46.4 (8.58)	0321 (0026)	0.331 (0.031)	0.148 (0.070)	103.0 (51.6)	0.951 (0.028)

α_w, sleep-to-wake transition time; γ_w, unitless wake allostatic magnitude in nmol/h; β, circadian amplitude; θ, circadian phase; d_c, cortisol disappearance rate; k_p, cortisol feedback constant; α_s, sleep allostatic magnitude in nmol/h; γ_s, unitless sleep allostatic rate.

consistently distributed across sleep scenarios. Finally, we cross-validated across study scenarios by comparing the fit generated by one group in a given scenario to the fit of the cortisol profile predicted by our model for a different study group undergoing the same scenario.

Individual and group mean model fits. For each of the three study groups, we obtained group mean model fits by first calculating a fit for each individual in the group and then averaging the individualized fits to determine the group mean fit. We used this procedure because the pulsatile secretions of cortisol are readily apparent in the individual data but obscured in the group mean data because of between-subject variations in the phase θ. For *group C*, we calculated its individuals' fits by simultaneously fitting the data from both scenarios to generate one set of parameter values for each individual.

Figure 3 shows the group mean fits for *group A* in the 0-h TAS scenario and *group B* in the 8-h TAS scenario. In the fitted mean cortisol concentration, the Mann-Whitney *U*-test showed that *group B* has a significantly lower concentration of cortisol from 2000 on *day 2* to 0000 on *day 3* ($P = 0.006$), corroborating the result in Ref. 22. Figure 4 shows the group mean fits for *group C* in the 4- and 12-h TAS scenarios. Figure 5 shows representative individualized fits for each of the four scenarios, which illustrate the pulsatile nature of cortisol concentration.

Table 1 shows the goodness of fit for the individualized fits and for each group mean fit, measured in terms of RMSE and r^2. The individual RMSE values were smaller for the 4- and 12-h TAS scenarios, whereas the group RMSE values were smaller for the 0- and 8-h TAS scenarios. Averaging over the four scenarios, the r^2 values indicated that the model accounted for 88% of the variance in the group mean data and 67% of the variance in the individual data.

Comparison of model parameters between groups. Table 2 shows the mean and standard deviation of each model parameter in each study group. The sleep allostatic parameters α_s and γ_s could not be determined for *group A* because they did not sleep in their scenario. Table 3 shows the *P* values calculated from Kolmogorov-Smirnov tests on the distributions of individualized parameters between study groups. Excluding the phase parameter θ, which is a state parameter (27) that depends on sleep-wake history and other environmental conditions, there are no statistically significant differences between the *group B* parameters and those of *groups A* and *C*. However, the parameters for *groups A* and *C* are significantly different. The significant differences between *groups A* and *C* suggest that the model is insensitive to the absolute amplitudes of the model's production parameters (α_w, β, α_s) and degradation parameters (k_p, d_c) because the estimates for all of these parameters are higher for *group A* than for *group C*. The model is more sensitive to the ratios between production and feedback parameters. Between *groups A* and *C*, *P* values calculated from Kolmogorov-Smirnov tests indicate that the distributions of the ratios α_w/k_p ($P = 0.18$) and β/k_p ($P = 0.25$) are not significantly different between the groups.

Cross-validation between study scenarios. We performed cross-validation by substituting the parameters for the individuals in *group C* into the models for the 0- and 8-h TAS scenarios and by substituting the parameters for the individuals in *group B* into the models for the 0-, 4-, and 12-h TAS scenarios. We did not perform cross-validation from *group A* onto the other study scenarios because sleep allostatic parameters were not available. To account for differences in cortisol amplitude across studies, we multiplied cortisol concentrations by 1.14 when cross-validating *group C* on the 0- and 8-h TAS scenarios and divided by 1.14 when cross-validating *group B* on the 4- and 12-h TAS scenarios. We determined the value 1.14 by taking the ratio of the grand mean cortisol level of *groups A* and *B* combined with that of *group C*. To account for differences in phase, we shifted the phase parameter θ by -1.02 h when cross-validating *group B* on the 0-h TAS scenario, by -0.77 h when cross-validating *group B* on the 4- and 12-h TAS scenarios, by -0.25 h when cross-validating *group C* on the 0-h TAS scenario, and by 0.77 h when cross-validating *group C* on the 8-h TAS scenario.

Figure 6 shows the adjusted group mean plasma cortisol fits. For model parameters from *groups B* and *C*, the Mann-Whitney *U*-test showed that the value of the fit onto the 8-h TAS scenario is significantly greater than the value of the fit onto the 0-h TAS scenario from 2000 on *day 2* to 0000 on *day*

Table 3. *P values resulting from 2-sample Kolmogorov-Smirnov tests on the distributions of parameter values calculated for each study group*

Model Parameters	Comparisons of Study Groups		
	Group A vs. *B*	*Group A* vs. *C*	*Group B* vs. *C*
α_w	0.21	**0.00012**	0.07
γ_w	0.017	**0.0036**	0.45
β	0.017	**0.0000064**	0.015
θ	**0.00022**	0.18	**0.0026**
d_c	0.58	**0.0000290**	0.0091
k_p	0.073	**0.00078**	0.9
α_s			0.044
γ_s			0.0091

Significant differences are in boldface. The Bonferroni-corrected threshold of significance is $P = 0.05 \div 8$. The significant differences in the distribution of θ can be attributed to adjustments in the circadian rhythm following 6 days of sleep restriction/extension or possibly seasonal differences in phase. The significant differences in the distributions of the parameters for *groups A* and *C* suggest that the model is insensitive to the absolute amplitudes of the model's production (α_w, β, and α_s) and degradation parameters (k_p, d_c), because the estimates for all of these parameters are higher for *group A* than for *group C*.

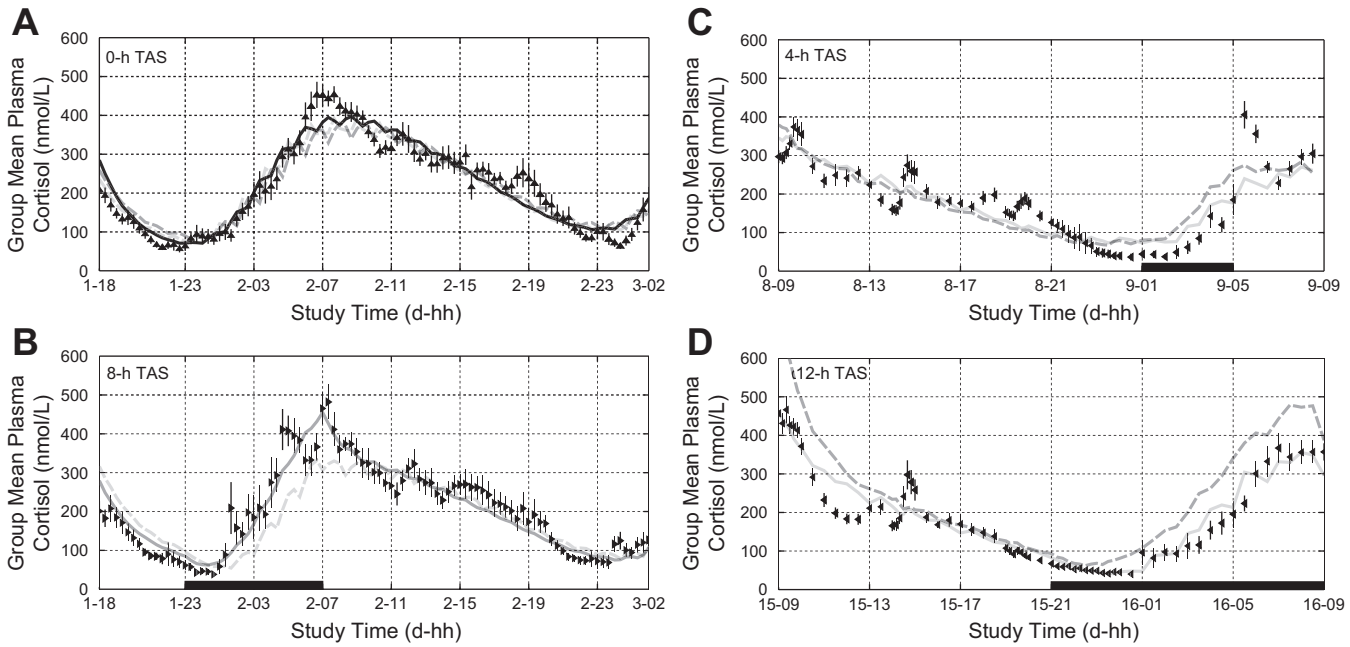

Fig. 6. Adjusted cross-validation fits between the different study scenarios: 0- (*A*), 8- (*B*), 4- (*C*), and 12-h TAS (*D*). The fits were adjusted with an amplitude adjustment factor of 1.14 to account for differences in study conditions and phase adjustments to account for differences in the group mean estimates of phase. Black line in *A* indicates the fit calculated from the *group A* parameters, the dark gray lines in *A–D* the fit from the *group B* parameters, and the light gray lines in in *A–D* the fit from the *group C* parameters. Solid lines indicate self-fits, and dashed lines indicate cross-validation fits. Black bars indicate the TAS. Figure 11 shows the unadjusted cross-validations. For model parameters from *groups B* and *C*, the Mann-Whitney *U*-test showed that the value of the fit onto the 8-h TAS scenario is significantly greater than the value of the fit onto the 0-h TAS scenario from 2000 on *day 2* to 0000 on day 3 ($P = 0.003$ for *group B*, $P = 0.0001$ for *group C*), in accord with the within-subject data reported in Ref. 9.

Table 4 shows the goodness of the cross-validation fits in terms of r^2, RMSE, and the *P* value from the Mann-Whitney *U*-test, which measures the probability that the fit has the same median as the data. The r^2 values for the cross-validation fits ranged from 52 to 90%, and the RMSE values ranged from 35.5 to 85.5 nmol/l. The relatively poor goodness of fit for the cross-validation from *group B* onto the 12-h TAS scenario was due to the fact that individuals in *group C* did not sleep for the whole 12 h; the average time asleep for individuals in the scenario was 9 h and 3 min (30).

DISCUSSION

We presented a phenomenological model that describes the effects of sleep duration on plasma cortisol concentration. We based the model on the Borbély two-process model of sleep regulation (3) and defined the amplitude of cortisol pulses as the combination of a sleep allostatic *process S*, a circadian *process C*, and a negative feedback term k_p. The structure of *process S* was inferred from the results of Gronfier et al. (16), which show a negative correlation between cortisol secretion rate and EEG-β power during sleep, and the results of Chapotot et al. (10), which show a positive correlation between the secretion rate and EEG-β power during wake. *Process C* was constructed using the standard parameters used Borbély and Achermann (4) for modeling sleep regulation. The proportional feedback term k_p is a simplified representation of cortisol's negative feedback mechanism (38) in which cortisol down-regulates the production of CRH and ACTH.

The phenomenological model predicts the decrease of cortisol concentration observed after the wake-to-sleep transition by Weitzman et al. (36) and the rapid increase in cortisol concentration before normal waking observed by Späth-Schwalbe et al.

Table 4. *Measurements of goodness of fit for the cross-validations*

	TAS, h											
	0			4			8			12		
Study Group	r^2	RMSE	*P*	r^2	RMSE	*P*	r^2	RMSE	*P*	r^2	RMSE	*P*
Group A	**0.91**	**34.2**	**0.67**									
Group B	0.90	35.5	0.78	0.74	50.2	0.96	**0.89**	**36.7**	**0.90**	0.52	85.5	0.04
Group C	0.88	39.3	0.54	**0.78**	**45.7**	**0.90**	0.68	61.9	0.58	**0.92**	**35.3**	**0.73**

Before these measurements were calculated, the fits were adjusted with an amplitude adjustment factor of 1.14 and phase adjustments to account for differences in the group mean estimates of phase. No adjustments were made to the cross-validation fits within studies. Values in boldface indicate self-fits. No cross-validations were made from *group A* onto other scenarios because the sleep allostatic parameters were unavailable. *P* is the *P* value from Mann-Whitney *U*-test. Bonferroni-corrected threshold for significance: $P < 0.05 \div 9$. Table 5 shows the values of these measurements for the unadjusted cross-validations.

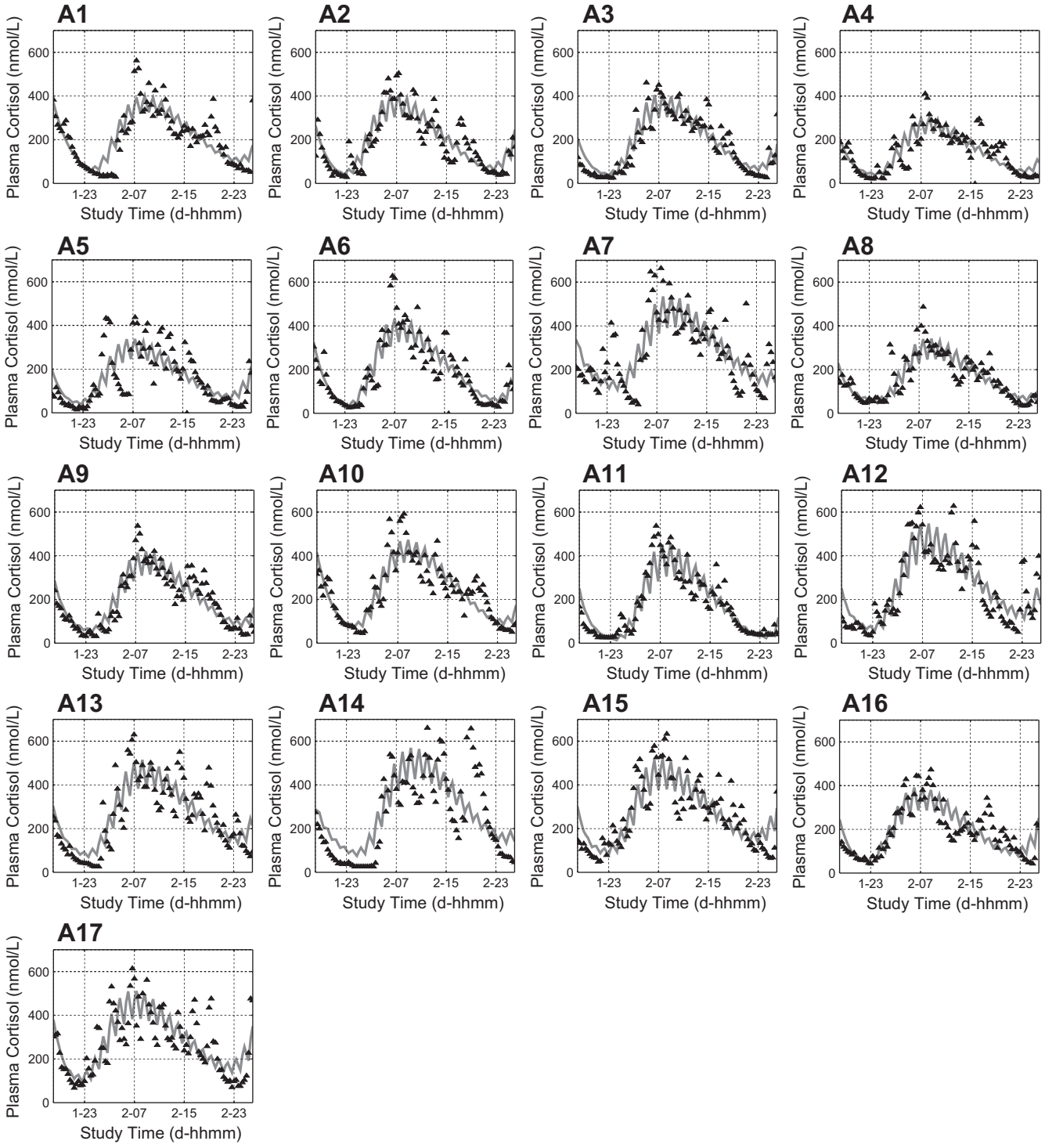

Fig. 7. Fits for each of the individuals in *group A* in the 0-h TAS scenario. *Subject 1* had the median root mean squared error among the 17 individuals, and the plot for *subject 1* from Fig. 7 is identical to the plot in Fig. 5*A*.

(29). Both of these phenomena are explained by the exponential form of *Process S* during sleep. At each wake-to-sleep transition, the sleep allostatic contribution to cortisol secretion drops to zero, leading to the decrease in plasma cortisol for 1–2 h after sleep onset observed by Weitzman et al. (36). Also, the estimated values of the sleep allostatic magnitude α_s predicted a rapid increase in the allostatic contribution to cortisol secretion after 5–8 h of sleep, leading to the rapid increase in concentration observed by Späth-Schwalbe et al. (29).

Notably, our model reconciles reports that there is no change in cortisol concentration as a result of total sleep deprivation (15, 28), with reports claiming that there is an increase (9, 22). The cause of the apparent discrepancy is the time of measurement. Follenius et al. (15) and Salín-Pascual et al. (28) measure the night

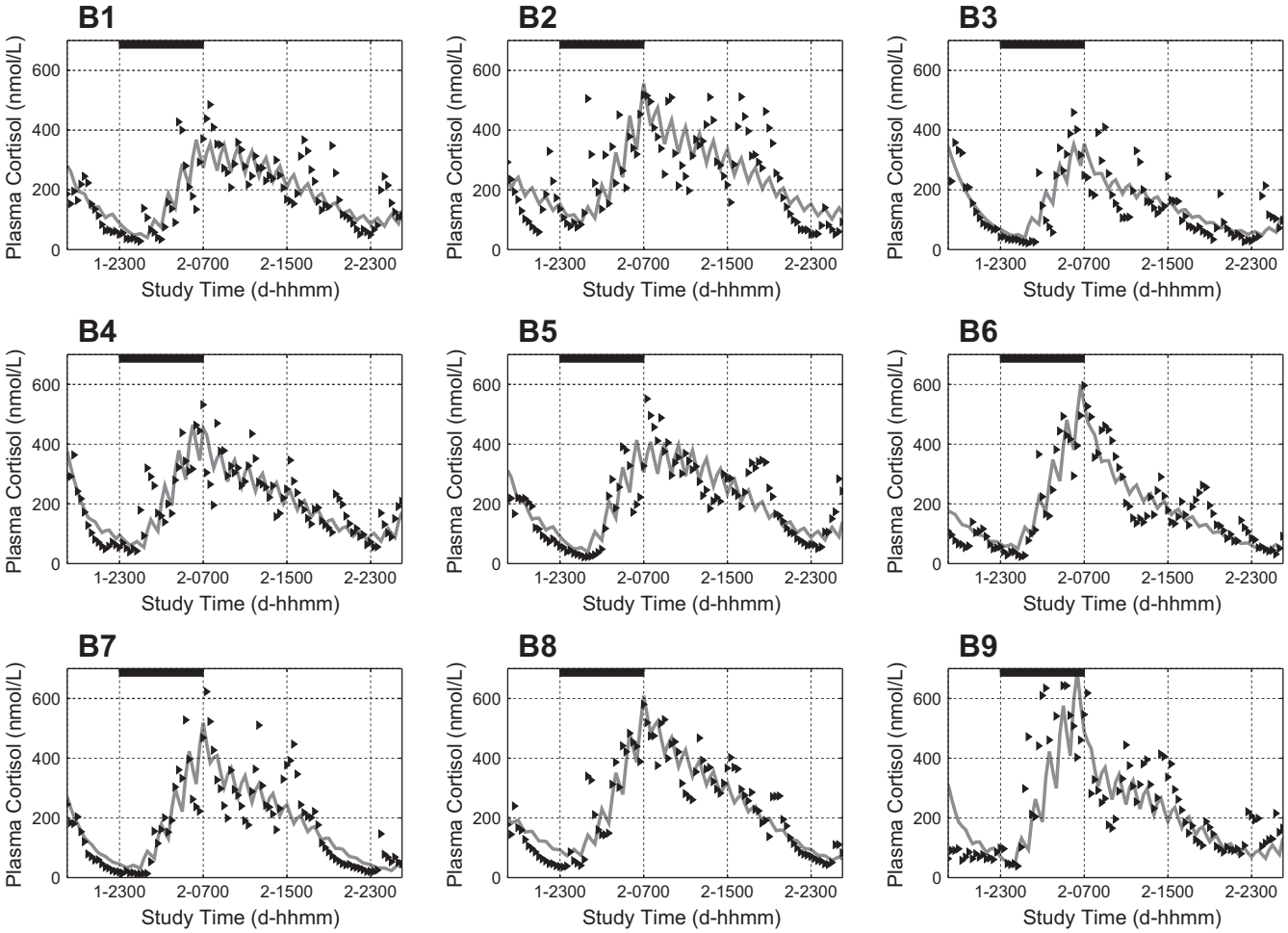

Fig. 8. Fits for each of the individuals in *group B* in the 8-h TAS scenario. *Subject 1* had the median root mean squared error among the 9 individuals, and the plot for *subject 1* from Fig. 7 is identical to the plot in Fig. 5*B*. Black bars indicate the TAS.

cortisol profile from 2300 to 0700 and from 2200 to 0600, respectively. During these hours, our model predicted that 8-h TAS individuals would experience a small decrease in cortisol concentration immediately after sleep onset as the contribution of the allostatic *process S* decreased to zero. However, because the sleep allostatic amplitude α_s was greater than the wake allostatic amplitude α_w (Table 2), the cortisol concentration of the sleeping individuals increased more rapidly than those of the awake individuals, leading to no significant total difference over the 8-h sleep period. In fact, our model predicted a slightly lower cortisol concentration in 8-h TAS individuals just after sleep onset and a slightly higher concentration just before waking, qualitatively mimicking the data of Salín-Pascual et al. (28). Whereas Leproult et al. (22) compared a 0-h TAS group and an 8-h TAS group and Chapotot et al. (9) reported on a within-subject study on the same group, both studies measured cortisol concentration for at least 11 h after waking. Our model predicted that differences in cortisol between *groups A* and *B* occur in the evening after sleep deprivation (Fig. 3). Also, we cross-validated *group B* onto the 0-h TAS scenario and observed that the predicted cortisol levels the following evening are greater than in the normal sleep scenario, in agreement with the within-subject results of Chapotot et al. (9) (Fig. 6).

To minimize the number of model parameters, we made several simplifying assumptions. First, we assumed a phase lock between the phase of cortisol secretion pulses and the phase of the circadian *process C*. Second, we assumed a simplified version of the cortisol autoregulation process. Instead of explicitly modeling the feedback mechanisms by which cortisol represses its precursors CRH and ACTH (38), we modeled the negative feedback loop with a single proportional constant, k_p. Third, we assumed a fixed interpulse period of 80 min, although this period can vary within and between individuals. By removing or modifying these assumptions, we could produce a more comprehensive but less parsimonious model.

The two-process model parameters show significant between-subject variability (Table 2). Some of this variability is due to the difficulty in estimating absolute values of both production and degradation parameters (Table 3), but there is significant variability between subjects that is caused by underlying physiological factors. Further investigation is necessary to relate the parameters from our model to the neuroendocrine parameters from mechanistic models (5, 13, 17, 20, 31). We hypothesize that between-subject variability in glucocorticoid receptor counts (34) could account for the

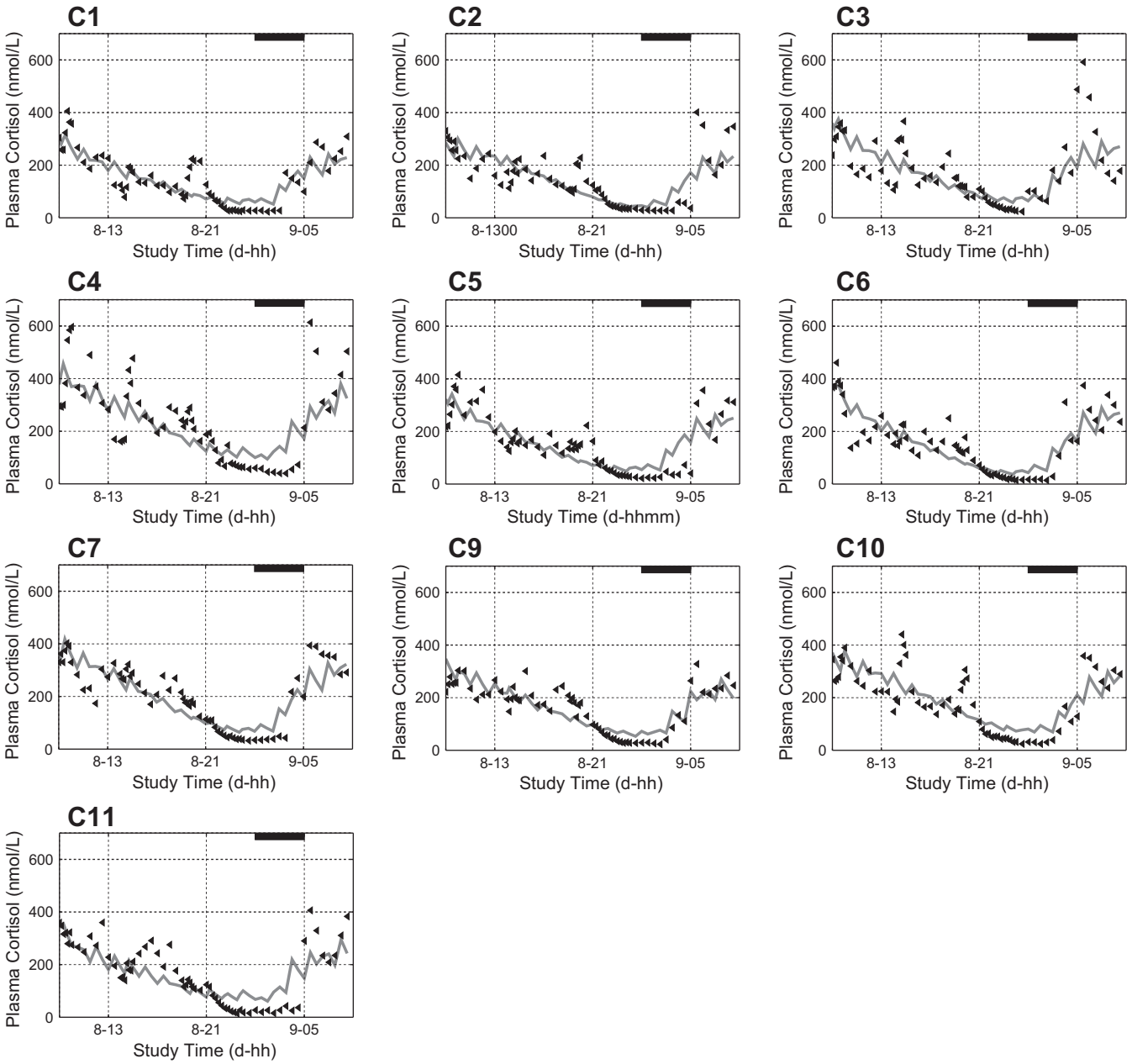

Fig. 9. Fits for each of the individuals in *group C* in the 4-h TAS scenario. *Subject 2* had the 6th largest root mean squared error among the 10 individuals, and the plot for *subject 2* from Fig. 7 is identical to the plot in Fig. 5*C*. Black bars indicate the TAS.

variability in the cortisol feedback constant k_p and disappearance rate d_c and that between-subject variability in the strength of the pulse generator in the pituitary (21) may be the cause of variability in the amplitude parameters α_w, α_s, and β. Differences in the CRH and ACTH secretion systems in the hypothalamus and pituitary may account for the variability in the rate parameters γ_w and γ_s. A possible confound affecting the distribution of the disappearance rate is the posture of the individual; the mean value we report for d_c yields a mean cortisol half-life of 105 min (SD = 19 min), slightly larger than the value reported in (14). However, this rate is likely affected by the recumbent posture of the individuals in the studies we considered (33).

Furthermore, the effects of the cortisol awakening response (26, 37) and of meals (33) are key phenomena not included in our model (1). The effect of the cortisol awakening response can be seen as a spike in both group mean and individual cortisol concentrations at the sleep-to-wake transition in the 4-h TAS scenario (Fig. 4), whereas the effect of meals can be seen in the postprandial increases in cortisol in *group C* (Fig. 3). Despite not explicitly modeling these phenomena that were observed only in the 4- and 12-h TAS scenarios, the goodness of fit of the model in terms of RMSE and r^2 was similar for all groups. However, the cortisol awakening response in particular has significant impact on the diurnal cortisol profile, and modeling this phenomenon will be essential to understanding how varying sleep durations impact the time course of cortisol concentration.

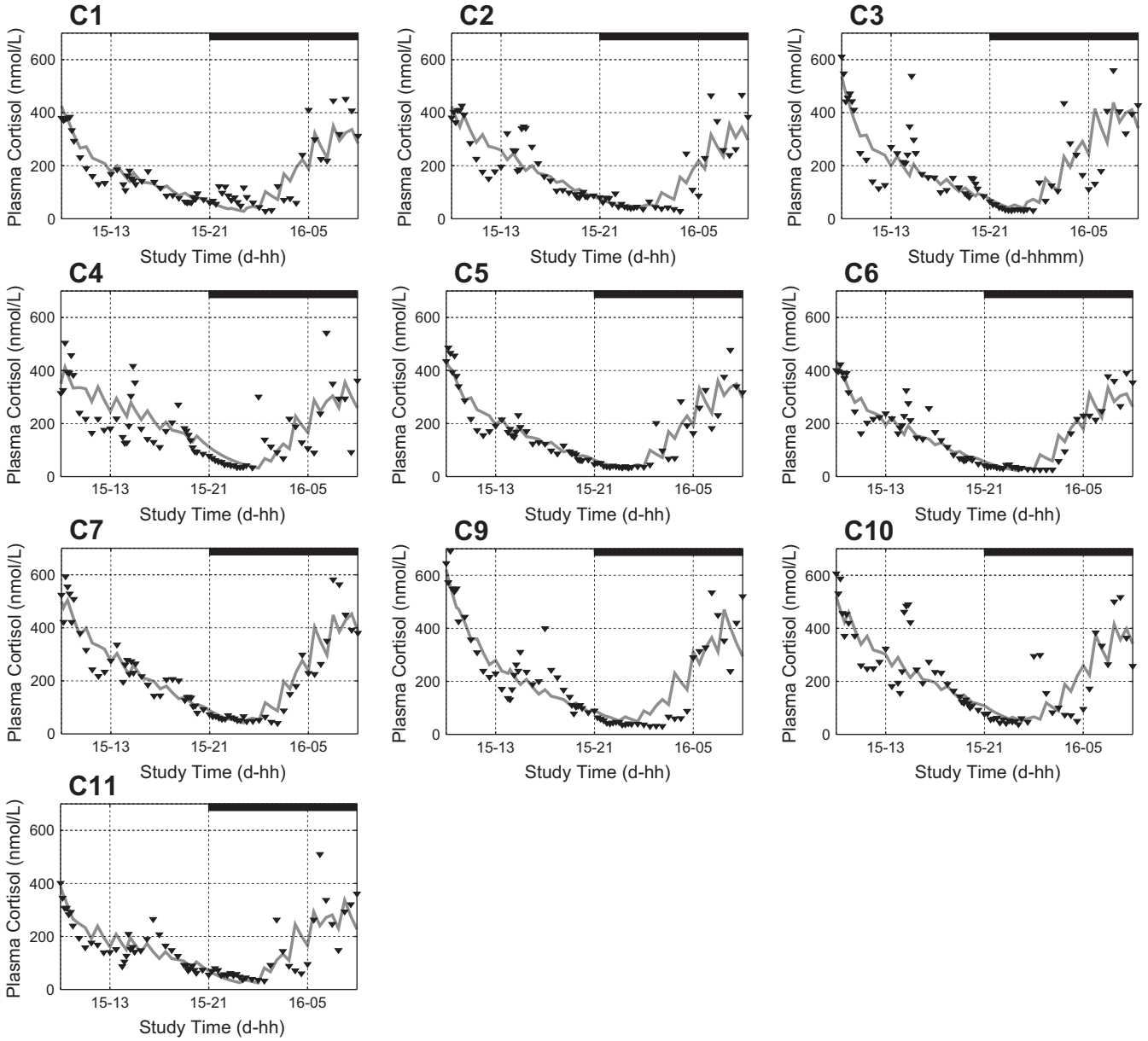

Fig. 10. Fits for each of the individuals in *group C* in the 12-h TAS scenario. *Subject 2* had the 6th largest root mean squared error among the 10 individuals, and the plot for *subject 2* from Fig. 7 is identical to the plot in Fig. 5*D*. Black bars indicate the TAS.

Further research is also needed to model differences in cortisol profiles due to sex and age (32), sleep shifting (7, 8), psychological disorders such as PTSD and depression, and metabolic disorders such as Cushing's syndrome (25). We expect that our phenomenological model will provide insight into these causes of between-subject variation in cortisol concentration and also have potential application to many other metabolites (12) and hormones that also display circadian rhythmicity.

APPENDIX

Figures 7, 8, 9, and 10 show the individualized fits for cortisol concentration for the 0-, 8-, 4-, and 12-h TAS, respectively.

Figure 11 shows the unadjusted group mean plasma cortisol fits wherein we did not account for differences in cortisol amplitude and circadian phase. Table 5 shows the goodness of the cross-validation fits in terms of r^2, RMSE, and the P value from the Mann-Whitney U-test. The r^2 values for the cross-validation fits ranged from -1 to 83%, and the RMSE values ranged from 46.8 to 123.5 nmol/l. The poor goodness of fit for the cross-validation from *group B* onto the 12-h TAS scenario was due to the fact that individuals in *group C* did not sleep for the whole 12 h, the difference in circadian phase between *group B* and *group C*, and the greater mean cortisol amplitude of *groups A* and *B* compared with *group C*.

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GRANTS

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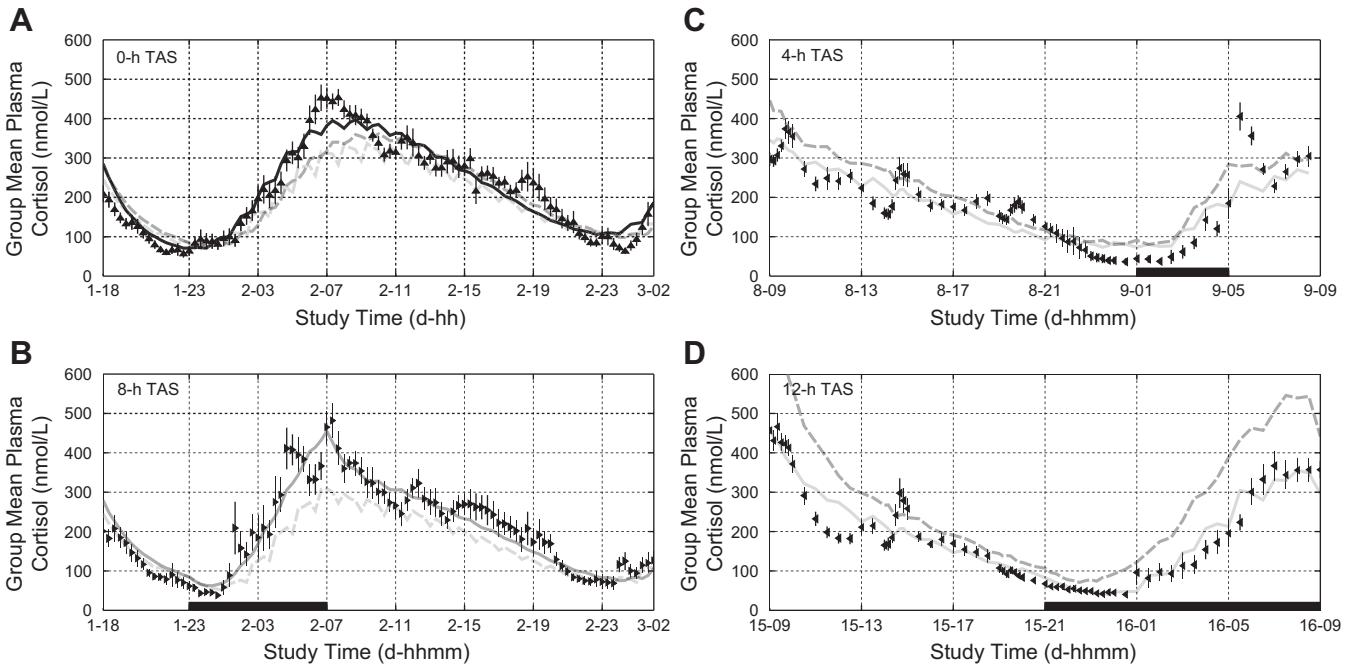

Fig. 11. Unadjusted cross-validation fits between the different study scenarios: 0- (*A*), 8- (*B*), 4- (*C*), and 12-h TAS (*D*). Black line in *A* indicates the fit calculated from the *group A* parameters, the dark gray lines in *A–D* the fit from the *group B* parameters, and the light gray lines in *A–D* the fit from the *group C* parameters. Solid lines indicate self-fits, and dashed lines indicate cross-validation fits. Black bars indicate the TAS for each scenario. Figure 6 shows the adjusted cross-validations.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The opinions and assertions contained herein are the personal views of the authors and are not to be construed as official or as reflecting the views of the US Army or the US Department of Defense. This article has been approved for public release with unlimited distribution.

AUTHOR CONTRIBUTIONS

D.T. and J.R. did the conception and design of the research; D.T. analyzed the data; D.T., R.L., and K.S. interpreted the results of experiments; D.T. prepared the figures; D.T. drafted the manuscript; D.T., R.L., K.S., and J.R. edited and revised the manuscript; D.T., R.L., K.S., and J.R. approved the final version of the manuscript.

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Table 5. *Measurements of goodness of fit for the cross-validations without amplitude or phase adjustment*

	TAS, h											
	0			4			8			12		
Study Group	r^2	RMSE	*P*	r^2	RMSE	*P*	r^2	RMSE	*P*	r^2	RMSE	*P*
Group A	**0.91**	**34.2**	**0.67**									
Group B	0.83	46.8	0.98	0.65	58.3	0.13	**0.89**	**36.7**	**0.90**	−0.01	123.5	0.004
Group C	0.78	53.4	0.3	**0.78**	**45.7**	**0.90**	0.63	66.9	0.02	**0.92**	**035.3**	**0.730**

Values in boldface are self-fits. No cross-fit was made from *group A* to the other scenarios because the sleep parameters were unavailable. *P* is the *P* value from Mann-Whitney *U*-test. Bonferroni-corrected threshold for significance: $P < 0.05 \div 9$. The poor performance of the cross-validations between *group B* and the 12-h TAS scenario was due to *1*) the difference between the amount of time in sleeping position and time spent actually asleep and *2*) the lack of matching between *groups A* and *B* and *group C*.

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